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PERSPECTIVE

Autoimmunity, Autoinflammation, and Infection in Uveitis



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- **PURPOSE:** To review the pathogenesis of uveitis in light of recent advances in our understanding of innate and adaptive immune responses and their regulation.
- **DESIGN:** Perspective.
- **METHODS:** Methods included a review of prevailing views on the pathogenesis of uveitis and an analysis of developments in immunology that impact on its conceptual basis, particularly the concept of immunologic tolerance and its loss in autoimmunity. Importantly, the role of infection in the pathogenesis of uveitis is evaluated.
- **RESULTS:** The results comprise a reappraisal of the pathogenesis of anterior vs posterior uveitis in the context of the blood-retinal barrier and its relation to autoimmune, autoinflammatory, and infectious uveitis. Autoimmunity is seen as a possible cause of certain forms of uveitis but definitive proof is lacking. Autoinflammatory disease, involving activated innate immune mechanisms, is considered causative in a second set of uveitis conditions. A place for infection in uveitis generally is proposed within a unifying concept for the pathogenesis of uveitis.
- **CONCLUSION:** Infection may be implicated directly or indirectly in many forms of noninfectious or *undifferentiated* uveitis. In addition to the growing recognition that foreign antigen, including reactivatable infectious agents, might hide within ocular tissues, the possibility that a dysregulated microbiome might generate T cells that cause immune-mediated ocular inflammation has now been demonstrated experimentally. An uncontrolled,

overexuberant host immune response may cause continuing irreversible tissue damage even after the infection has been cleared. (Am J Ophthalmol 2018;189:77–85. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)).

UVEITIS IS A THREAT TO VISION, EITHER DIRECTLY or through ocular complications.¹ With a prevalence of 115–204 per 100 000 population and incidence of 17–52 new cases/100 000 per year in Northern California, uveitis is infrequent but, because it affects all age groups, carries a significant socioeconomic burden.² Uveitis specialists categorize uveitis etiologically as either infectious or noninfectious.³ Infections are proven causes of some cases of uveitis.^{4–7} In others, activation of innate immune processes in response to infection may cause tissue damage through a mechanism of autoinflammation.

Noninfectious uveitis is not synonymous with autoimmune uveitis. The autoimmune hypothesis for noninfectious uveitis derives from experimental models of retinal inflammation that create blood-retinal barrier (BRB) breakdown and stimulate adaptive immunity directed toward retinal antigenic targets. In nonretinal tissues, autoinflammatory or innate immune-mediated mechanisms may prevail. Because infectious agents usually drive autoinflammation, infection may underlie the pathogenesis of most uveitis, either through cytolytic tissue damage or through uncontrolled and dysregulated host immune responses that continue after infection subsides.

This perspective discusses evidence to support the concept that infection may be *more* and autoimmunity *less* involved in the pathogenesis of uveitis.

KEY ROLE OF BLOOD-RETINAL BARRIER IN UNDERSTANDING THE PATHOGENESIS OF UVEITIS

UVEITIS AS A UNIVERSAL TERM IS NOT ACCURATE regarding pathogenesis, as other ocular components are

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often the inflammatory target. However, the uvea is consistently involved in intraocular inflammation, transporting more than 80% of the ocular blood volume, as well as managing the bulk flow of aqueous fluid.⁸ The clinical classification of uveitis based on anterior, intermediate, posterior, or panocular location³ is insufficient when considering the pathogenesis of uveitis, which depends on whether the BRB is breached. Uveitis may be restricted to tissues external to the BRB, encompassing iritis, cyclitis, keratouveitis, sclerouveitis, and choroiditis, or uveitis may affect tissues normally protected by the BRB, including retinitis, retinal vasculitis, retinochoroiditis, and optic neuritis. In pathogenetic terms, *posterior uveitis* involves breakdown of the BRB while other forms of uveitis do not. Inflammation that involves compromise of the BRB is always associated with inflammation of the uveal tract, but the reverse is not true. This distinction helps us to understand the etiology of uveitis.

IS NONINFECTIOUS UVEITIS AUTOIMMUNE?

AUTOIMMUNITY HAS BEEN PROPOSED AS THE PATHOGENESIS for noninfectious uveitis,⁹ paralleling the accepted pathogenesis of other organ-specific autoimmune diseases.^{10,11}

In principle, an autoimmune disease requires the identification of an autoantigen and an experimental model that resembles human disease.¹² Although both lens protein and uveal pigment have been proposed as potential autoantigens,¹³ extensive experimentation with uveal extracts has failed to produce a reliable animal model that mirrors human uveitis. The retina contains several potent autoantigens that are expressed in the thymus¹⁴ and in secondary lymphoid tissue,¹⁵ where immunologic tolerance and prevention of autoimmune disease is maintained by a range of mechanisms, including clonal deletion and anergy. Genetic defects in the autoimmune regulator (AIRE) gene¹⁶ are known to cause experimental and clinical autoimmune diseases, including a form of posterior uveitis.¹⁷ Regulatory T cells (Treg) also maintain self-tolerance and control immune responses,^{18,19} including those in the retina.^{20,21} Autoimmunity to retinal autoantigens can be induced in several animal models, including primates.¹⁷ Experimental autoimmune uveitis (EAU) is considered a classical organ-specific autoimmune disease that resembles posterior uveitis in humans.²² Despite the many insights that EAU reveals into mechanisms of tissue damage in posterior uveitis, the model is difficult to translate to the wide range of human uveitic entities.

In EAU, there is extensive breakdown of the BRB^{23,24} with release of retinal autoantigens. Depending on context, these have the potential to activate the small number of self-antigen reactive T cells that have escaped thymic deletion and circulate in the periphery.¹⁵ Accord-

ingly there is a marked expansion of autoreactive T cells and autoantibodies to retinal antigens that can be detected in mice with EAU. Similar cellular or humoral immunologic evidence is required to define autoimmune uveitis in humans. However, despite genetic conditions such as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy/dysplasia (APECED),¹⁶ evidence for autoimmunity in undifferentiated noninfectious uveitis is sparse. Some clinical entities that are linked closely with restricted MHC genetic types such as Vogt-Koyanagi-Harada (VKH) disease,²⁵ sympathetic ophthalmia,^{26,27} and birdshot retinochoroidopathy (BRC)²⁸ have the strongest claim to be *bona fide* autoimmune diseases. Of these, BRC may resemble diabetes mellitus as a potential CD8 T cell-mediated autoimmune disease in which presentation of cryptic peptide determinants of retinal S antigen²⁹ could theoretically be enhanced by presentation *via* HLA A29.³⁰

Several studies have demonstrated that both humoral and cellular responses to a range of retinal antigens and their epitopes occur in patients with either infectious or undifferentiated uveitis.^{31–33} Results have been inconsistent and self-reactivity to retinal antigens has been observed in healthy individuals.^{32,34–37} Similar confounding results have been observed in nonocular diseases, and the number of definitive autoimmune diseases, in which autoreactive T cells or autoantibodies have been shown to be pathogenic, is limited. In addition, restoration of immunologic tolerance in patients with diseases such as multiple sclerosis, rheumatoid arthritis, and uveitis, although clearly effective in experimental models³⁸ that use experimental therapies such as mucosal tolerance induction, has not yet reached the clinic.³⁹

Alternatively, a reduction in Tregs has been viewed as evidence that regulation of autoimmunity is impaired. However, the situation is complex. Circulating Tregs may be reduced in active disease but paradoxically may be increased in the tissues in both uveitis and rheumatoid arthritis.⁴⁰ The plasticity of Tregs and their possible interconversion with pathogenic T cells has also not helped to define immunoregulatory mechanisms.⁴¹ In addition, because Tregs can control immune responses to both autoantigens and infectious agents¹⁸ their involvement does not help to differentiate autoimmune disease from postinfectious immune-mediated disease.

The above observations do not exclude autoimmune pathogenesis. For instance, autoimmune pathology may be part of a dual process arising later in disease evolution, such as via bystander damage in which release of autoantigen during an infectious condition leads to activation of autoreactive T cells. Indeed, most recently peptide therapy with the autoantigenic peptide proinsulin in patients with early type 1 diabetes has been shown to delay progression of disease, as measured by insulin requirement.⁴² Perhaps a consistently identifiable target retinal autoantigen might allow a peptide therapy approach for secondary autoimmunity in human uveitis.

TABLE 1. Autoinflammatory Monogenic Disorders and Uveitis

Condition	Gene Affected	Mechanism	Uveitis ^a	Reference
Familial Mediterranean fever (FMF)	Pyrin (<i>MEVF</i>)	Increased inflammasome activity	Yes	43
HIDS	Mevalonate kinase (<i>MVK</i>)	Increased inflammasome activity	Reviewed by Ter Haar	44
Muckle-Wells syndrome	<i>NLRP/cryopyrin</i>	Inflammasomopathy	Yes	45
CAPS	Cryopyrin	Inflammasomopathy	yes	46
TRAPS	TNF receptor 1 (<i>TNFRSF1A</i>)	Protein misfolding	? (periocular inflammation)	47
NOMID	<i>NLRP/cryopyrin</i>	Inflammasomopathy	Yes	48
Blau syndrome	<i>NOD2/CARD 15</i>	NF- κ B dysregulation	Yes	49
Pyoderma gangrenosum and acne	<i>PSTPIP1/CD2BP1</i>	PSTPIP1 \rightarrow pyrin binding	No	50
Deficiency in IL-1 receptor antagonist	IL-1RN	Absence of IL-1Ra	No	
Majeed syndrome	Lip2 (<i>LIPIN2</i>)	? NLRP regulation defect	No	^b
HLH	<i>UNC13D</i> , perforin, syntaxin	Macrophage activation	Yes	51
Gaucher disease	<i>GBA</i> (acid glucosidase)	?	Yes	52
Aicardi-Goutier syndrome	Trex (<i>TREX1</i>)	Failure of cDNA sensing by RIG-1	Chorioretinitis in Aicardi-like syndrome reported	53
CANDLE syndrome	<i>PSMB8</i>	Proteasome subunit defect	yes	54

CAPS = cryopyrin-associated periodic syndrome; HIDS = hyperimmunoglobulinemia D and periodic fever syndrome; HLH = hemophagocytic lymphohistiocytosis; NOMID = neonatal-onset multisystem inflammatory disease; TRAPS = tumor necrosis factor-associated periodic fever syndrome.

^aUveitis, predominantly anterior, contributes to the overall phenotype of several monogenic autoinflammatory disorders.

^bNo direct association with uveitis.

IS NONINFECTIOUS UVEITIS AUTOINFLAMMATORY?

AUTOINFLAMMATION AND AUTOINFLAMMATORY DISEASE are relatively recent concepts based on observations that patients with monogenic disorders affecting innate immune cells (predominantly myeloid cells such as macrophages and neutrophils) developed discrete syndromes, such as TNF receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever (FMF) (Table 1). Innate immune cells are central to classical autoimmune diseases owing to their essential role in generating adaptive immunity (described by Janeway as “the immunologist’s dirty little secret”⁵⁵). Animal models of autoimmunity, including EAU, require a bacterial adjuvant to stimulate innate immune cells, particularly dendritic cells (DC),⁵⁶ which in turn activate specific T cells.⁵⁷ Pattern recognition receptors (PRR) recognize classes of microorganisms by interaction with molecular patterns on pathogens (PAMPs) and then generate a range of T cells including Th1, Th17, and Th9, ordinarily thought of as part of the adaptive immune system.⁵⁸

TRAPS was the first reported autoinflammatory disease in humans. Its defining features are episodes of unprovoked ocular, periocular, and skin inflammation in the absence of high titers of autoantibodies or T-cell responses. The condition results from spontaneous production of cytokines owing to a missense mutation in p53, one of the proteins

in the NF- κ B complex.⁵⁹ Since then, several other autoinflammatory conditions have been described (Table 1) and, as with discoveries relating to adaptive immunity, in which delineating the genetic defects in patients with T- and B-cell abnormalities revealed their physiological function,⁶⁰ mutations in genes controlling innate immune pathways have greatly assisted our understanding of how innate immunity is structured. Several classes of PAMPs have now been discovered, which activate specific signaling pathways through PRRs for bacteria, fungi, viruses, parasites, and other foreign organisms and when these pathways are spontaneously activated, or homeostatic control dysregulated, they cause autoinflammatory diseases (Table 1).

Since many cases of uveitis are episodic, are unprovoked, and lack good evidence for specific autoantibodies or T-cell responses to support an autoimmune pathogenesis, it has been suggested that at least some forms of uveitis may be autoinflammatory. Many monogenic autoinflammatory conditions involve activation of the inflammasome and are characterized by the secretion of IL-1 or one of its related molecules.⁶¹ Importantly, skin/mucosal pathology in the form of vesicles or ulceration is almost a common denominator. Uveitis features as part of the syndrome in several of these conditions⁶² (Table 1). Moreover, the definition of autoinflammatory disease has been widening to an increasing list of complex genetic disorders, which includes type 2 diabetes, macular degeneration, and Behçet disease (Table 2).

TABLE 2. Multisystem Disorders With Possible Autoinflammatory Pathogenesis and Their Association With Uveitis

Condition ^a	Gene(s)	Mechanism	Uveitis (Reference)
Systemic-onset JIA	?	? macrophage activation and IL-1a gene	63, 64
Adult-onset Still's disease	?	? overproduction of IL-1beta	^b
Schnitzler syndrome	? sporadic	Increased inflammasome activation	^b
Crohn disease	<i>NOD2/ATG16L1 IGRM</i>	NF-kB dysregulation	65
CRMO	?	? anti-IL-6 responsive	^b
SAPHO	?	? deficiency in FOXO1	66, 67
Gout	<i>SLC2A/GLUT9/ABCG2</i>	Crystallopathy	68
Pseudogout	?	Crystallopathy	^b
Type 2 diabetes	?	Glucose → inflammasome activation	^b
Atypical hemolytic uremic syndrome	<i>CFH, CD46, CFI, CFB</i>	Abnormal regulation of C3b	^b
Age-related macular degeneration	<i>CFH</i>	Failed inactivation of C3b, inflammasome activation	^b
Behçet disease	?	Increased inflammasome activation	69, 70
Atherosclerosis	?	? dysregulated macrophage activation	^b
Asbestosis	?	Particles → inflammasome activation	^b
HLA B27 spondyloarthropathies	MHC class I (<i>HLA B27</i>)	Misfolded protein → inflammasome activation	71

CRMO = chronic recurrent multifocal osteomyelitis; JIA = juvenile idiopathic arthritis; SAPHO = synovitis-acne-pustulosis-hyperostosis-osteitis.

^aAn increasing number of polygenic, multisystem diseases may have an autoinflammatory pathogenesis; uveitis, both posterior and anterior, is a prominent feature of some of these conditions.

^bNo direct association with uveitis.

A closer examination of uveitic conditions reveals some that might fit the description of autoinflammation, in which there is evidence of activation of innate immune (myeloid) cells in the absence of a specific trigger. Some of these are polygenic systemic conditions in which uveitis may be part of the clinical presentation (Table 2). Candidate diseases include Behçet disease, juvenile idiopathic arthritis (JIA)-associated anterior uveitis, pars planitis, intermediate uveitis, and tubulointerstitial nephritis/uveitis syndrome, as well as others in which no autoantigen has been identified, there are no representative animal models, and clinical evidence for humoral or cell-mediated autoimmunity is thin. In particular, the HLA B27-associated spondyloarthropathies, and presumably by association HLA B27-linked acute anterior uveitis, are considered by some to be autoinflammatory diseases⁷² with a predisposition linked to protein misfolding and IL-23 polymorphisms.⁷³ Both anterior and posterior uveitis occur in Behçet disease, which resembles an autoinflammatory disease by its predominantly neutrophil-mediated pathology.⁷⁴

Pathogenetically, it is unlikely that the full range of heterogeneous uveitis conditions can be attributed to autoinflammatory mechanisms. In this evolving field, unlabeled conditions with a positive response to blockade of IL-1 are preliminarily described as *undifferentiated* systemic autoinflammatory diseases.⁷⁵ Similarly, noninfectious uveitis has been rebranded as *undifferentiated* uveitis to signify the lack of a clear etiology.⁷⁶ In this context, uveitis associated with Behçet disease⁷⁷ and JIA has been reported to respond to anti-IL-1 therapy in small cohort studies. A

larger study using the same criteria to investigate a range of non-Behçet posterior uveitis was inconclusive.⁷⁸ Despite the current uncertainty, increasing knowledge of the molecular signatures of disease seems likely to improve our understanding of the heterogeneity of uveitis.

IS NONINFECTIOUS UVEITIS CAUSED BY INFECTION?

INFECTIOUS AGENTS HAVE BEEN IMPLICATED IN THE PATHOGENESIS of autoimmune and autoinflammatory diseases generally. There is also a long-standing suspicion that the morbidity that results from many forms of ocular inflammatory disease derives from infection, either directly or by a dysregulated host response to infection. Noninfectious uveitis or undifferentiated uveitis is described as immune-mediated when no direct infectious cause can be identified but may in fact have been initiated by infection.

How infection might underpin the pathogenesis of uveitis relates to experimental models of autoimmune disease. Like most experimental models, EAU, a paradigmatic autoimmune disease,¹⁷ requires mycobacterial extract and pertussis toxin to prime autoantigenic (IRBP)-specific Th1 and Th17 T cells, which target the retina and cause the disease. The mycobacterial extract commonly used to induce EAU is H37Ra which is an attenuated form of *Mycobacterium tuberculosis* (MTb) cultured from tissue samples of a patient with active tuberculosis.⁷⁹ MTb is rich in PAMPS and activates the inflammasome and other

pathways to release proinflammatory cytokines such as IL-12, IL-23, IL-27, and IL-1. IL-1, the major cytokine driving autoinflammatory disease (see above section), is required for EAU induction by activating DC.⁸⁰ In contrast, tolerogenic DC, which protect experimental mice against EAU, specifically fail to generate IL-1 when activated by MTb.⁸¹

MTb is believed to have infected up to a third of the world's population, the majority of whom remain latently infected, with a significant mortality rate.⁸² MTb is a major cause of uveitis in humans, both in developed and in developing countries,^{83,84} and presents in a large variety of clinical phenotypes, some of which are included in the category undifferentiated or noninfectious, such as atypical serpiginous choroiditis.⁸⁵ How might MTb cause ocular inflammation? During the initial infection in the lung, myeloid cells (macrophages and DC) are specific targets of MTb that either kill or are killed by the MTb. In other cells, MTb evades killing and becomes latent within the cell. Latently infected myeloid cells traffic in and out of granulomas⁸⁶ and recirculate to reside in extrapulmonary sites such as the kidney, dermis, muscle, lymph nodes, meninges, and uveal tract, where they can be reactivated at later times. If the pathogen thrives, a severe local infection with tissue damage (eg, caseation) ensues. However, if the pathogen is contained, as in an immunocompetent individual, an overexuberant host immune response to the reactivated MTb might then cause severe immune-mediated damage. In addition, at extrapulmonary sites of tissue damage, MTb antigen released from dead cells might act as a local adjuvant to innate immune cells that stochastically interact with autoreactive T cells in a bystander fashion and cause a secondary autoimmune reaction. Recent evidence for this secondary autoimmune reaction in patients with tuberculous uveitis has been reported.⁸⁷

A link with infection or infectious material is difficult to identify in many cases, either clinically or experimentally. For instance, spontaneous models of EAU occur in retinal antigen-specific T cell-receptor transgenic mice without use of adjuvant.⁸⁸ However, exposure to microbial antigen still appears to be necessary, since EAU fails to develop in these mice if they are bred in germ-free conditions.⁸⁹ In fact, even the standard model of IRBP/MTb adjuvant-induced EAU cannot be induced in germ-free mice.⁹⁰ Remarkably, it appears that commensal antigen from the bowel activates antigen-specific T cells, which traffic to the retina and cause disease. These observations have considerable significance for the long known association between inflammatory bowel disease, uveitis, and the spondyloarthropathies. Interestingly, not all commensal antigen is harmful; some commensals appear to protect from uveitis and so the context, and possible association with dysbiosis, might determine whether infection-associated immune-mediated uveitis occurs.⁹¹ These clinical and experimental observations suggest that noninfectious, undifferentiated uveitis may be initiated by persistent, nonreplicating microorganisms or residual microbial antigen. The infectious

etiology of chronic anterior uveitis caused by *Propionibacterium acnes* may not be immediately recognized. Similarly, recurrent chronic anterior uveitis owing to herpes viruses often fails to yield active virus on investigation. Other forms of previously undifferentiated anterior and posterior uveitis are now recognized as being attributable to infection, such as hypertensive uveitis caused by cytomegalovirus (CMV); Fuchs heterochromic uveitis due to rubella; and chikungunya virus, West Nile virus, dengue virus, and *Rickettsia* as causes of retinal vasculitis.

Much of the evidence for infection in these cases is not based on strict criteria of demonstrating replicating virus, but is simply based on viral DNA detected in ocular fluid or on serologic evidence of a prior infection. As such, direct causative relationships between the infection and uveitis cannot be established but an adjuvant or, at least, an immune-mediated role whereby persistent antigen drives reactivation of resident memory T cells^{92,93} can be envisaged. Recurrent uveitis might thus result either from reactivated replicating infectious agent or from a reactivated host immune-mediated response to an infectious agent. This has particular relevance, for instance, to uveitis associated with tuberculosis or toxoplasmosis where both antimicrobial therapy and immune-modulating agents may be required to minimize tissue damage but risk reactivating the latent microorganism. In some cases viable replicating microbial agents have been demonstrated. The recent reports of late cultured virus from ocular and other tissue samples in patients who have recovered from Ebola, Zika, and other viral infections indicate that viable virus persists in the tissues for long periods.^{94–96}

This may be a common mechanism for the pathogenesis of disease—namely that if the host survives the initial infection and the infectious agent is not completely cleared, then, to varying degrees, the organism persists undetected, either as a viable infectious agent or as a residual antigenic pool, which allows recurrent immune-mediated recrudescence of anti-microbe and/or anti-host (bystander effect) tissue damage. Perhaps an “either-or” approach to the pathogenesis of uveitis in terms of infection is too restrictive and a greater role for pathogens, either as a direct effect (infectious uveitis) or as the cause of a dysregulated host response to pathogens once they have either been cleared or become latent (noninfectious, undifferentiated uveitis), offers a more unified pathogenetic framework.

DOES THE BLOOD-RETINAL BARRIER REGULATE BOTH INFECTIOUS AND NONINFECTIOUS/UNDIFFERENTIATED UVEITIS?

AS ARGUED IN THE FIRST SECTION OF THIS PERSPECTIVE, the pathogenesis of posterior uveitis, affecting the retina

and optic nerve, is different from uveitis affecting sites outside the BRB. Retinal and CNS antigens are *protected* from damage by the BRB, which in the immunocompetent, healthy individual prevents both invasion by infectious agents and the passage of potentially damaging immune cells. It does this through 2 mechanisms: a physical barrier composed of the tight junctions of the retinal blood vessels and the retinal pigment epithelium (RPE), and an immunologic barrier formed by cells of the neurovascular unit (retinal endothelium, perivascular macrophages, pericytes, microglia, and the foot processes of glial cells forming the glia limitans)^{97,98} and by the RPE. The RPE in particular produces immunosuppressive mediators and, importantly, converts naïve T cells to Treg.^{99–101}

Immune regulation at the BRB applies to both infectious and noninfectious uveitis. For example, infectious forms of uveitis that occur outside the BRB, such as CMV- and HSV-induced anterior uveitis, do not involve the retina unless the patient has lost immune regulatory control at the BRB. Thus, a CD4 count <50 cells/mL in untreated AIDS patients allows unchecked viral replication and CMV retinitis. When the CD4 count rises above 50, viral replication and infection in the retina can be controlled but if the Treg/T-effector^{102,103} cell ratio is not normalized, cell immune-mediated uveitis ensues. Only if the BRB is physically broken or immunologically impaired, as has been shown repeatedly in experimental animal models,¹⁰⁴ can viral retinitis be induced.

The BRB presents both a physical and an immunologic barrier to infectious agents and to circulating immune cells, and it serves in this capacity for both infectious uveitis, in which damage is caused directly by the infecting agent, and noninfectious immune-mediated uveitis, in which an uncontrolled, dysregulated immune response is the cause. An appropriate immune response that adequately clears any infection is clearly desirable. Regulating the host

cellular immune response to the infectious agent or to an autoantigen, before either the infectious agent or the tissue damaging immune cells can cross the BRB, is also essential. Most infectious agents, particularly viruses and parasites, are held in check by the BRB but have ready access to other ocular tissues and cause uveitis either by replicating in situ in the acute phase or by inducing chronic/recurrent immune-mediated inflammation. In contrast, infectious agents that manage to cross the BRB either cause massive replicative end-stage damage or become latent (as in toxoplasmosis), mainly owing to effective immunoregulatory mechanisms of the retinal parenchymal microenvironment.

CONCLUSION

THERE IS A GROWING AWARENESS THAT WHILE EXAMPLES of autoimmune and autoinflammatory mechanisms have been well described and may explain the pathogenesis of uveitis, many cases of idiopathic or undifferentiated uveitis may ultimately be seen to be initiated by infection. Chronic inflammation and tissue damage may be the result of an exaggerated or dysregulated host response to the infection and the microbiome might be a significant source of infectious antigen and antigen-specific T cells. Thus, chronic or recurrent uveitic disease may be caused by local reactivations of persistent microbial agents or inadequately cleared antigen, including retroviral antigen, which intermittently disrupt the Treg/T-effector cell ratio. In addition, a dysregulated microbiome may predispose to, or even be the source of, uveitogenic pathogens or adjuvants. Indeed, it is also likely that periodic episodes of uveitis in monogenic autoinflammatory diseases are driven by microbes that would normally be harmless in immunocompetent individuals.

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